

## Case Report

# An Unusual Presentation of Primary Cutaneous Aggressive Epidermotropic CD8+ T Cell Lymphoma

Mihai Lupu<sup>1</sup>, Vlad Voiculescu<sup>1,2</sup>, Laura Papagheorghe<sup>1</sup>, Cornelia Nițipir<sup>2,3</sup>,  
Ana Maria Neagu<sup>2,4</sup>, Liliana Gabriela Popa<sup>1,2</sup>, Călin Giurcăneanu<sup>1,2</sup>

<sup>1</sup>Elias Emergency University Hospital, Department of Dermatology

<sup>2</sup>“Carol Davila” University of Medicine and Pharmacy, Bucharest

<sup>3</sup>Elias Emergency University Hospital, Department of Oncology

<sup>4</sup>Elias Emergency University Hospital, Department of Hematology

## REZUMAT

### *Limfomul cutanat cu celule T CD8+ agresiv epidermotrop - prezentare atipică*

**Introducere:** Limfomul primar cutanat agresiv epidermotrop cu celule T CD8+ este un tip foarte rar de limfom citotoxic cu o tendință crescută de extensie la situsuri extraganglionare, răspuns slab la terapiile convenționale pentru limfoamele cutanate cu celule T CD4+ și prognostic nefavorabil.

**Prezentare de caz:** Prezentăm cazul unui pacient în vârstă de 40 ani care s-a internat în clinica noastră pentru papule și plăci infiltrate, ulcerate, acoperite de cruste necrotice generalizate și ulcerații dureroase acoperite de depozite albe la nivelul palatului moale și dur în evoluție de 18 luni. Tabloul clinic și histopatologic particular au ridicat reale dificultăți diagnostice și terapeutice, pacientul fiind diagnosticat inițial cu papuloză limfomatoidă, apoi cu limfom cutanat cu celule T și tratat cu methotrexate, retinoizi aromatici orali și fototerapie, fără beneficiu clinic. În timpul spitalizării în clinica noastră a fost stabilit diagnosticul de limfom primar cutanat agresiv epidermotrop cu celule T CD8+ și a fost instituit tratament cu ciclofosamidă și dexametazonă, asociat cu iradiere locală. Deși leziunile cutanate și orale s-au ameliorat în primele 3 luni de tratament, afecțiunea s-a agravat progresiv ulterior.

**Concluzii:** Dată fiind paucitatea datelor din literatura de specialitate, prezentările atipice frecvente, comportamentul agresiv și lipsa strategiilor terapeutice optime, limfomul primar cutanat agresiv epidermotrop cu celule T CD8+ continuă să reprezinte o provocare diagnostică și terapeutică. Publicarea de noi prezentari de caz, comunicarea experienței clinice și a rezultatelor diverselor regimuri terapeutice ar putea ajuta la clarificarea definiției, clasificării și ar ghida managementul acestor forme de limfom cutanat foarte agresiv.

**Cuvinte cheie:** limfom cutanat, agresiv, chimioterapie

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**Corresponding author:**

Cornelia Nițipir, MD

Elias Emergency University Hospital, Department of Oncology

e-mail: nitipir2003@yahoo.com

## ABSTRACT

**Background:** Primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma is an extremely rare type of cytotoxic lymphoma with increased tendency of spreading to extranodal sites, poor response to conventional therapies for classic CD4+ cutaneous T cell lymphomas, and an unfavorable prognosis.

**Case report:** We present the case of a 40 year old male patient who was referred to our clinic for generalized ulcerated, escharotic, infiltrated papules and plaques and painful ulcerations covered by white deposits on the soft and hard palate of 18 months duration. The unique clinical and histopathological features had posed great diagnostic and therapeutic difficulties. The patient had first been diagnosed with lymphomatoid papulosis, and later with T cell lymphoma and treated with methotrexate, oral retinoids and phototherapy without clinical benefit. During hospitalization in our clinic, the diagnosis of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma was established and treatment with cyclophosphamide and dexamethasone, associated with local radiation therapy was instituted. Although the cutaneous and oral lesions improved during the first 3 months of treatment, the condition gradually worsened afterwards.

**Conclusions:** Due to the paucity of literature data, frequent atypical presentations, aggressive behavior, and lack of optimal treatment strategies, primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma continues to represent a diagnostic and therapeutic challenge. Further case reports that describe clinical experience and therapeutic outcomes would help clarify its definition, classification and guide the management in this very aggressive cutaneous lymphoma.

**Key words:** cutaneous lymphoma, aggressive, chemotherapy

## BACKGROUND

Primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma is an extremely rare type of cytotoxic lymphoma reported for the first time by Berti et al. in 1999, (1) who described the tumor as a distinct clinico-pathologic entity with an aggressive clinical course. It presents as widespread, rapidly evolving papules, plaques, and tumors, often showing central necrosis and ulceration, histologically characterized by epidermotropism of CD8+ CD4- T cells. The condition has an increased tendency of spreading to extranodal sites, usually responds poorly to conventional therapies for classic CD4+ cutaneous T cell lymphomas (CTCLs), and has an unfavorable prognosis. (1-4)

Primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma is classified as a provisional, ill-defined, but stand-alone entity within a heterogeneous group of "primary cutaneous peripheral T cell lymphoma, unspecified" according to the World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification (2005) and the 4th Edition of the WHO classification (2008). (5-7)

The diagnosis is based on the integration of clinical, histological, and immunohistochemical data. However, some patients do not present with classic

skin lesions and do not have a typical course from the disease onset,(6) and others exhibit atypical clinical features throughout the evolution of the disease,(2) leading to diagnostic difficulties. Therapy is usually determined by the stage and clinical extent of the disease. In addition, no therapeutic regimen able to control the very aggressive course of this disease and improve the very low associated survival rate is yet available.(1,6)

Herein, we discuss the case of a patient suffering from primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma who presented with unique clinical and histopathological features that posed great diagnostic and therapeutic difficulties, showing modest response to cyclophosphamide and dexamethasone chemotherapy.

## CASE REPORT

We present the case of a 40 year old male patient who was referred to our clinic after an 18 months history of generalized, ulcerated, escharotic, infiltrated papules, plaques and tumors (**Fig. 1, 2**). Painful erosions and ulcerations covered by white deposits on the soft and hard palate were also present (**Fig. 3**). The patient suffered from diabetes mellitus (currently treated with oral antidiabetics - Metforminum 1g bid) and obesity (BMI= 31



**Figure 1.** Ulcerated, infiltrated papules and plaques on the posterior torso



**Figure 2.** Ulcerated, infected tumors on the face

kg/sqm), was a heavy smoker (20 pack-year), but denied regular alcohol consumption.

The skin lesions first appeared 18 months earlier on the posterior torso and were represented by pruritic, erythematous papules and plaques covered by very fine scales. In the absence of a specific treatment, new similar lesions appeared on the face, neck, arms, and abdominal area. They grew in size, ulcerated and became infected. Moreover, the patient developed oral, nasal and genital ulcerations.

Five months after the onset of the disease, a punch biopsy was performed, the histopathological exam confirming the clinical suspicion of lymphomatoid papulosis. Treatment with methotrexate 15 mg/week, folic acid 5 mg/week and phototherapy was instituted, but only led to minor clinical improvement, therefore it was stopped after approximately 1 year. At that moment, the thoracic and abdominal computed tomography (CT) scan revealed the presence of a 6 mm pulmonary nodule, hepatomegaly and infracentrimetric subdiaphragmatic adenopathies.

The patient was referred to a hematology specialist, who established the diagnosis of cutaneous T cell lymphoma without systemic involvement. A new skin biopsy was performed and once again, the histopathological diagnosis was that of follicular lymphomatoid papulosis. The histological examination was not completed at that time by immunohistochemical analysis. The patient was treated with acitretin 10 mg qid and tacrolimus ointment applied once daily. After experiencing no clinical improvement under this treatment, the patient was referred to our clinic.

At presentation, skin examination revealed multiple polymorphic skin lesions including ery-



**Figure 3.** Ulceration covered by white deposits on the hard palate

thematous papules and plaques with central ulceration, necrosis, and crusting, and pyoderma gangrenosum-like lesions. The lesions were painful and generalized. A small, less than 2 cm in diameter, firm, nonadherent, painless right axillary adenopathy was found. The rest of the clinical examination did not yield any pathologic findings.

Based on the medical history and clinical examination a preliminary diagnosis of cutaneous T cell lymphoma was made.

The complete blood count did not show any abnormal findings and the basic metabolic panel was normal. A peripheral blood flowcytometry was performed and revealed no malignant T-cell lymphocyte population. Contrast head-chest and abdominal CT scan only showed enlarged bilateral axillary lymph nodes, and no supra- or subdiaphragmatic adenopathies. Serology for hepatitis B and C viruses, human immunodeficiency viruses 1 and 2, and human T cell lymphotropic virus 1 (HTLV-1) was negative.

An incisional skin biopsy revealed a wide area of ulceration, fibrin and leukocyte debris with marked tumoral infiltration comprised of medium and large cells that presented with marked nucleocytoplasmic pleomorphism, tachichromatic and hypertrophic nuclei, chromatin in heaps and frequent mitosis, enlarged capillaries and intricate erythrocyte extravasations. The histopathological diagnosis was that of large cell non-Hodgkin's lymphoma.

Immunohistochemical stains were performed on formalin fixed, paraffin-embedded tissue sections. Lymphocytes were CD3 and CD8 positive, with showed partial loss of CD7. The CD8/CD4 ratio was approximately 2,1. Lymphocytes were negative for CD5, CD20, and CD30, thus excluding anaplastic large T cell lymphoma.

A Hematology-Oncology assessment was performed. In contrast to the extension of skin lesions, there was no proof of systemic involvement at that time. However, considering the severity of the skin lesions, evolving despite systemic and local therapy, the Hematology/Oncology board recommended conservative treatment with local radiation therapy and chemotherapy using Cyclophosphamide and Prednisone as pulse-therapy.

During the first 3 months of treatment, the clinical condition gradually improved, and resolution of the irradiated lesions was achieved. No new lesions appeared. However, after 3 months of treatment, new erythematoviolaceous papules and plaques started to appear on the patient's face, neck, chest, abdomen, limbs and genitalia. These lesions grew into large tumors that subsequently ulcerated and crusted. Numerous painful hemorrhagic and non-hemorrhagic bullous lesions appeared on his palms and soles. The lesions soon became infected and the patient's general condition declined. The oral lesions worsened, impairing alimentation. The patient refused therapy, left the hospital against medical advice and did not return for follow-up.

## DISCUSSION

Cutaneous T cell lymphomas (CTCL) are a heterogeneous group of diseases with various clinical presentations, outcomes, histological and immunohistochemical features. (2) According to the WHO-EORTC classification, primary cutaneous epidermotropic CD8+ T cell lymphoma, first described in 1999, (1) represents less than 1% of CTCL cases. (7) Patients with primary cutaneous aggressive epider-

motropic CD8+ T cell lymphoma are usually adults. A slight male predominance has been noted. Typically, patients present with rapidly progressive, widely distributed papules, plaques, nodules and tumors, often showing central ulceration, hemorrhage or necrosis. Lesions can occur on different skin areas, with acral regions and mucosal surfaces commonly affected. (6,8) Systemic spread to extracutaneous sites such as lung, brain, and testis is frequent, whereas lymph nodes are usually spared. (1,3,6) Rare presentations such as hyperkeratotic patches and plaques resembling Ketrone-Goodman type pagetoid reticulosis, (2) widespread annular erythematous scaling patches, papillomatous plaques and nodules, (9) rapidly spreading maculopapular eruption, (10) and pyoderma gangrenosum-like lesions (11) have also been reported.

This case represents one of the few reported cases to present with multiple pyoderma gangrenosum-like lesions distributed especially on the trunk and frank bullous lesions. These rare clinical pictures of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma should be kept in mind when dealing with cases of pyoderma gangrenosum lesions or immunobullous diseases resistant to standard therapies.

Tumor cells are pleomorphic small-medium or medium-large T cells accompanied by reactive macrophages and dendritic cells, a small number of eosinophils and plasma cells. (1) Sometimes immunoblasts predominate. (5,6) Typical rimming of adipocytes was noted in some cases of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma, but it was not apparent in our patient.

The aggressive course of the lesions and the concomitant presence of prominent epidermotropism help differentiate this disease from subcutaneous panniculitis-like T cell lymphoma (SPTCL), in which rimming of adipocytes is considered a characteristic morphologic feature. (12) As in all aggressive cutaneous lymphomas, invasion and destruction of adnexal skin structures are commonly seen. Angiocentricity and angioinvasion may also be present. (13) All of these characteristics were found in our case, indicating its very aggressive nature.

Immunophenotyping of tumor cells usually reveals positive CD3, CD8, bF1, granzyme B, perforin, TIA-1 and CD45RA, and negative CD4, CD20, and CD45RO, whereas CD2, CD5, CD7, and CD56 have variable expression profiles. (1,5,6) In the present case and in the original description by Berti

et al., (1) staining for CD56 was negative. However, cases with positive staining for CD56 have also been reported. (14)

In summary, our case was clinically characterized by the presence of classic lesions in addition to unique features, including the combination of severe pyoderma gangrenosum-like and bullous skin lesions, involvement of the entire body surface and of mucosal surfaces, marked deterioration of the patient's general condition. Severe keratinocyte necrosis, intraepidermal and subepidermal blisters were particular histological features.

For a stepwise diagnosis of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma, it is very important to exclude mycosis fungoides (MF). Classic MF usually has a more prolonged course and progresses over years from patches to plaques and, finally, to tumors, does not affect the general condition of the patient, and has a low tendency to systemic spread, therefore having a good overall prognosis.

By contrast, primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma is not characterized by longstanding precursor lesions and does not follow the typical progression of MF but, rather, presents from the start with widespread, often ulcerated, plaques and tumors, has a high tendency to systemic spread, and is usually associated with a poor prognosis.(1,2,4,6)

The differential diagnosis should also include other CD8+ dermatoses. Pagetoid reticulosis, CD30+ primary cutaneous anaplastic large-cell lymphoma, lymphomatoid papulosis, nasal and extranasal natural killer (NK)/T cell lymphoma, SPTCL, cutaneous  $\gamma/\delta$  T cell lymphoma, and rare cases of MF or S $\alpha$ ry syndrome may all express CD8+ phenotype.(2,6) These subtypes of CTCL share numerous histological and immunohistochemical features with primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma, but they can be differentiated by their clinical picture, their indolent course, and low tendency to systemic spread. Differential diagnosis is important as it helps avoid overdiagnosis and, consequently, overtreatment because the non-aggressive subtypes usually respond to conventional, less toxic therapies such as psoralen combined with ultraviolet A (PUVA). Aggressive epidermotropic CTCL, on the other hand, does not respond to skin-directed therapies and often requires polychemotherapy. (1,6)

The prognosis of patients with primary cutaneous

aggressive epidermotropic CD8+ T cell lymphoma is very poor, with a median survival time of 32 months.(1,3) This may be attributed to delayed diagnosis caused by limited awareness of this recently described subtype of CTCL, the aggressive behavior of the cutaneous lesions, particularly ulcerated lesions, the common tendency to metastasis to unusual extracutaneous sites including the lung, testis, and central nervous system, and the unresponsiveness and/or worsening that may result from the use of conventional therapies for CTCL, such as interferons.(3,6) In the present case, the absence of metastatic spread represented an interesting finding considering the fact that the patient presented to our clinic one year after disease onset. Systemic involvement, angiocentricity and angioinvasion, and the expression of CD56, CD15, and the CD7-/CD2+ phenotype have been proposed to be associated with poorer prognosis.(3,5,6)

It is difficult to define the best treatment regimen for primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma due to the small number of reported cases and the lack of clinical trials. Patients with early patch/plaque MF are candidates for skin-directed therapies such as photodynamic therapy with or without interferon alpha, imiquimod, topical chemotherapy, ionizing radiation or systemic biologic response modifiers, including retinoids. Moreover, the disease represents a therapeutic challenge because conventional therapies used for classic CD4+ CTCL, such as interferon- $\alpha$ , are ineffective and may actually worsen the condition, which already exhibits a T helper (Th) 1 cytokine profile. Activated Th1 responses increase the recruitment and proliferation of CD8+ T cells. (2,6,15) Total skin electron beam irradiation in combination with the administration of oral retinoids, such as bexarotene, is the regimen preferred by some clinicians, (6,14,16) though not available in our country. However, long-term remission has not yet been established,(6) and a rapid onset of CD8+ aggressive T cell lymphoma has been reported during bexarotene therapy in a patient with S $\alpha$ ry syndrome.(15) Systemic polychemotherapy, usually a doxorubicin-based regimen (e.g. cyclophosphamide, doxorubicin, vincristine, prednisone - CHOP) is often required, but the highly aggressive nature of the tumor and the common systemic spread make it very resistant to even the most combative regimens.(3,5,6,15) Gemcitabine, a purine analog without high immunosuppressive

activity, may be a suitable chemotherapeutic agent for this aggressive tumor, which is usually associated with severe immunodeficiency.(6) Some systemic agents for CD4+ CTCL approved by the FDA, such as denileukin diftitox or histone deacetylase inhibitors may also prove effective against aggressive epidermotropic CD8+ T cell lymphoma. (6) A promising new treatment option could be represented by allogeneic or autologous transplantation, either alone or in combination with other therapies.(16) Hyper-CVAD chemotherapy has been used without definite success in some cases of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma.(17)

Our patient received three cycles of cyclophosphamide and dexamethasone (CD) initially with a clinical benefit – no new skin lesions, good clinical status, without overall satisfactory results in terms of both his general condition and the cutaneous lesions. The same regimen was unsuccessful in a case reported by Gormley et al.,(6) although this may be explained by the delay in starting therapy, at one year after the initial diagnosis, when metastatic spread had reached the lung; in the present case, therapy was initiated immediately after diagnosis before any metastatic spread had occurred.

## CONCLUSIONS

Due to the paucity of literature data, the atypical presentations seen in some cases, the aggressive behavior, and the absence of optimal treatment strategies, primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma continues to represent a diagnostic and therapeutic challenge. No single clinical, histological or immunohistochemical feature alone is pathognomonic for this disease. However, in light of the multiple histological and immunohistochemical overlaps with other indolent types of CD8+ CTCL, we believe that the clinical features and highly aggressive behavior of primary cutaneous aggressive epidermotropic CD8+ T cell lymphoma are crucial for the diagnosis.

Further case reports that describe clinical experience and therapeutic outcomes in this very aggres-

sive variant of CTCL would help clarify its definition and classification and furthermore make it easier to promptly diagnose and treat these patients in order to achieve the most favorable prognosis possible.

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